Appeal No. 2009-1270
(Serial No. 09/719,045)

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

IN RE ANDREW PAUL CHAPMAN AND DAVID JOHN KING

Appeal from the United States Patent and Trademark Office,
Board of Patent Appeals and Interferences.

BRIEF FOR APPELLEE – ACTING DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

RAYMOND T. CHEN
Solicitor

FRANCES M. LYNCH
JANET A. GONGOLA
Associate Solicitors

P.O. Box 15667
Arlington, Virginia 22215
(571) 272-9035

Attorneys for the Acting Director
of the United States Patent and
Trademark Office

August 5, 2009

1. A divalent antibody fragment comprising

[a] two antibody heavy chains and

[b] at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage,

[c] each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.

A272 (brackets added).

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STATEMENT OF RELATED CASES

(a) The Acting Director is not aware of any other appeal from the Board of Patent Appeals and Interferences ("Board") for the United States Patent and Trademark Office ("USPTO") in connection with this application that has previously been before this or any other Court.

(b) The Acting Director is also not aware of any pending case in this or any other Court that will directly affect, or be directly affected by, this Court's decision in this appeal.

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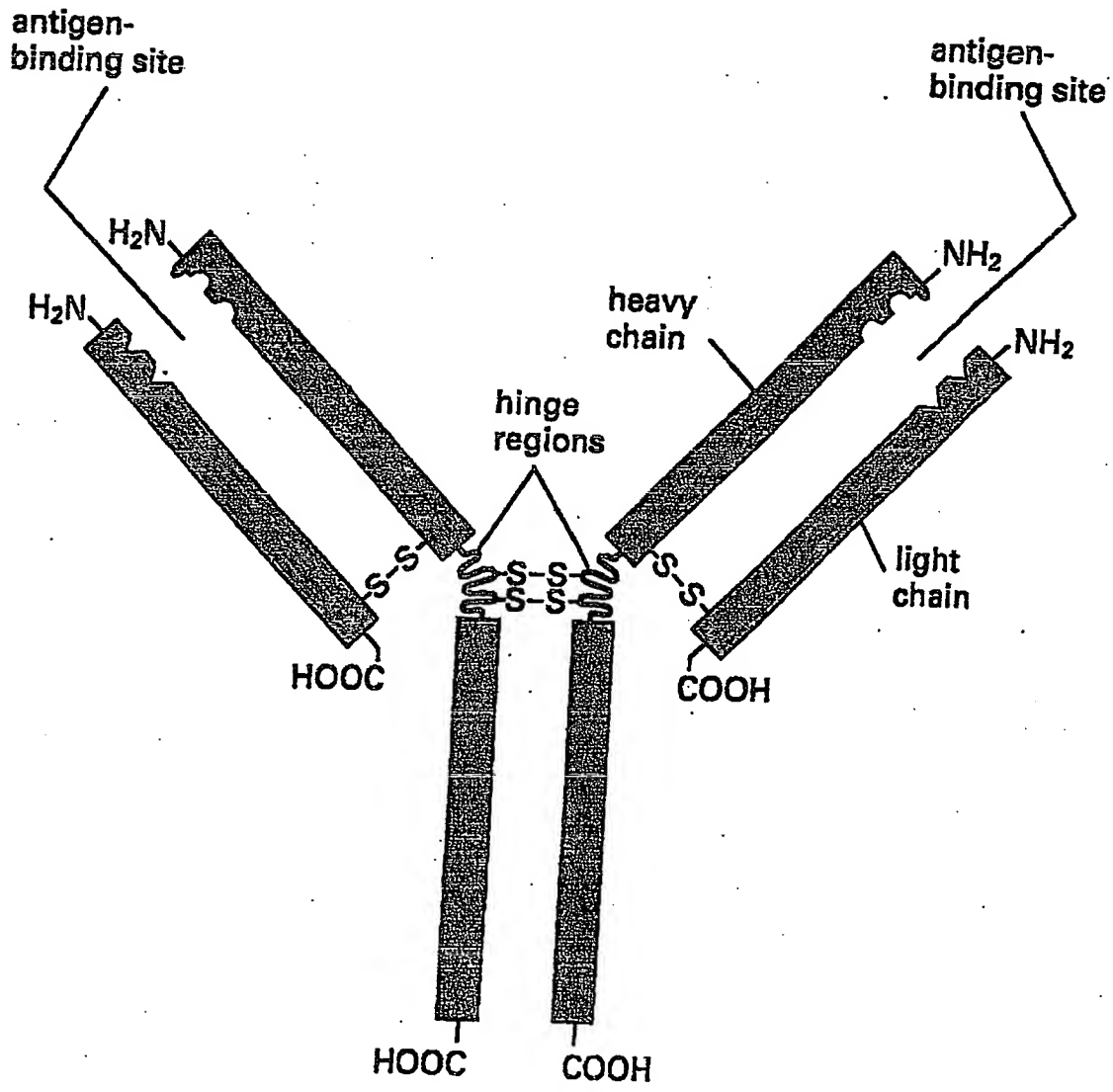
I. STATEMENT OF THE ISSUE

Chapman claims a "dumbbell-shaped" divalent antibody fragment made by linking a polymer between cysteine residues in each heavy chain. Chapman also claims that each cysteine residue is located outside the variable region of each chain. Chapman further claims that the polymer functions to increase the circulating half-life of the antibody fragment.

Gonzalez discloses linking two antibody fragments with a polymer to form a "dumbbell-shaped" structure. Elsewhere in his specification, Gonzalez teaches that the preferred site to link a polymer to an antibody fragment is a cysteine residue outside the variable region. Gonzalez further discloses that the polymer increases the circulating half-life of the antibody fragment.


antigen-
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H_2N
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The main question on appeal is whether the Board correctly concluded that one of ordinary skill would have combined Gonzalez' disclosure of a dumbbell-shaped antibody fragment-polymer conjugate with Gonzalez' teaching of a preferred polymer attachment site to arrive at Chapman's claimed invention.

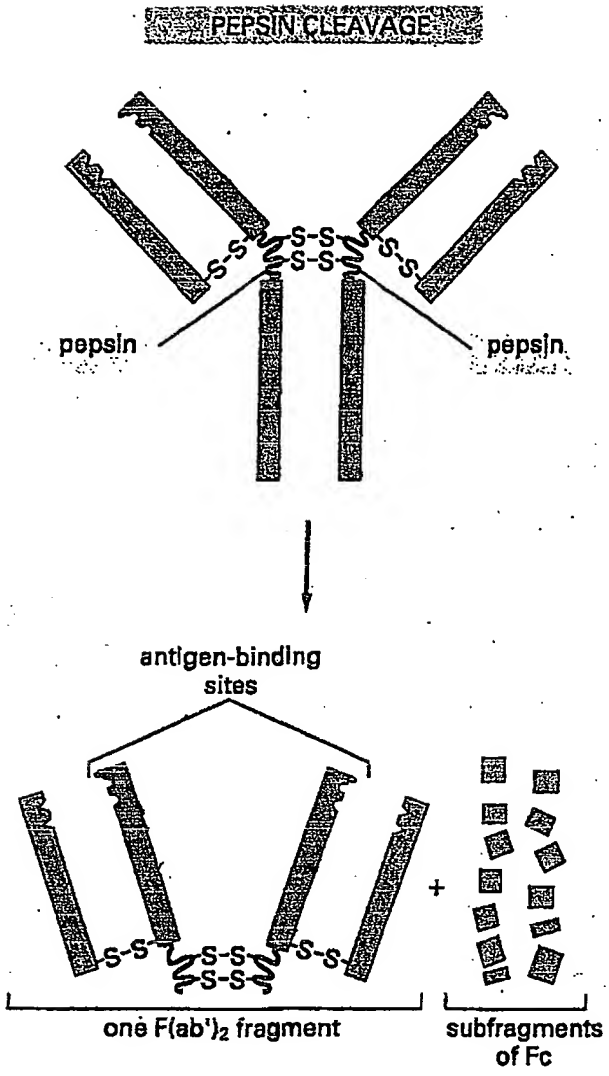
II. STATEMENT OF THE CASE

This case involves U.S. Patent Application No. 09/719,045 entitled "Divalent Antibody Fragments." On May 27, 2008, the Board affirmed the examiner's final rejection (A279-299) of claims 1-10, 12, 13 and 15 as obvious over Gonzalez and also claims 1, 13 and 14 as obvious over the combined teachings of Gonzalez and Barbanti. A1-18. On reconsideration, the Board maintained its rejections. A19-23. This appeal followed.

III. STATEMENT OF THE FACTS

A. Technology at Issue

Antibodies are proteins made of amino acids. Antibodies bind tightly to antigens to inactivate them. See Bruce Alberts, et al., Essential Cell Biology, 145 (Garland Science) (2d ed. 2004). As shown in the figure on the facing page, antibodies are "Y"- shaped and have two identical light chains and two identical heavy chains. See Bruce Alberts, et al., Molecular Biology of the Cell, 1207-1208 (Garland Publishing, Inc.) (3d ed. 1994); see also Chiron Corp. v.


PEPSIN CLEAVAGE
pepsin
pepsin
antigen-binding sites
one F(ab')2 fragment
subfragments of Fc

Genentech, Inc., 363 F.3d 1247, 1250 (Fed. Cir. 2004). More specifically, each arm of the Y-shape is formed by one light chain linked to a heavy chain via a disulfide bridge. Id. at 1209. The two arms are joined to each other and to the stem of the Y at the hinge region via additional disulfide bridges. Id. A disulfide bridge is formed by the covalent bond between two sulfur atoms from the thiol (-SH) groups in the amino acid cysteine on each chain. Each heavy and light chain has a variable region, which is the antigen binding region. See Chiron, 363 F.3d. at 1250.

As shown in the figure on the facing page, an antibody can be digested by an enzyme called pepsin that cuts the antibody below the arms to generate a $F(ab')_2$ fragment, which is dumbbell-shaped. See Bruce Alberts, et al., Molecular Biology of the Cell at 1208-9. A $F(ab')_2$ fragment is "divalent" because it has two antigen binding sites, one at the end of each arm. Id. An antibody can also be digested into two F(ab) fragments by a different enzyme called papain, breaking the disulfide bridge between the arms. Id. A F(ab) fragment is "monovalent" because it has only one antigen binding site. When the F(ab) fragment has at least one cysteine residue in the hinge region, it is denoted as F(ab'). A553, col. 11, ln. 59-62. The F(ab') fragment is designated as F(ab')-SH when the cysteine residue(s) have a free thiol group. Id. at ln. 62-64.

B. Chapman's Claimed Invention: Antibody Fragment Linked To a Polymer to Increase Circulating Half-life

Chapman's representative claim 1 is directed to a divalent antibody fragment comprised of two heavy chains covalently linked by at least one non-disulphide interchain bridge. A272. The non-disulphide interchain bridge indirectly links the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue of the other chain via the intervening polymer, which is "effective for increasing the circulating half-life" of the antibody fragment. A272. Each cysteine residue is located outside the variable region of each heavy chain. A272. Chapman does not dispute the examiner's characterization of Chapman's claimed antibody fragment as being "dumbbell-shaped." A 284; Br. at 20-23.

The Board treated claims 1, 13 and 14 as representative. A3. In this appeal, Chapman has waived any separate argument regarding the Board's conclusion that claims 1, 13 and 14 are obvious over Gonzalez and Barbanti. Br. 6, 20. Thus, the sole issue on appeal is whether representative claim 1 is obvious over Gonzalez. Claim 1 recites:

A divalent antibody fragment comprising

[a] two antibody heavy chains and

[b] at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage,

> [c] each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.

A272 (brackets added).

C. The Prior Art

1. Gonzalez

Gonzalez [1] describes linking antibody fragments to a polymer to increase the amount of time that the antibody fragment remains in circulation in the body, i.e., the antibody fragment's circulating half-life. A411, Abstract; A548, col. 1, ln. 13-19; A555, col. 15, ln. 15-24. Gonzalez recognizes that the prior art established that a polymer, PEG, "attached to a sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule." A548, col. 1, ln. 38-43. Thus, Gonzalez explains that antibody fragment-polymer conjugates are desirable as "viable alternatives to intact antibodies used for therapeutic treatment of many disease indications." A555, col. 15, ln. 32-36.

[1] Nucleic Acids Encoding Humanized Anti-IL-8 Monoclonal Antibodies, U.S. Patent No. 6,025,158 (filed Feb. 20, 1998) (issued Feb. 15, 2000) (A411-648).

Gonzalez discloses: (1) a single antibody fragment linked to a polymer(s); (2) a dumbbell-shaped structure made up of two antibody fragments joined by a polymer; and (3) a "rosette" or other shaped structure composed of more than two antibody fragments joined by a polymer(s). A565, col. 35, ln. 38-57.

Gonzalez teaches how to prepare antibody fragment-polymer conjugates. Gonzalez identifies Fab, Fab', Fab'-SH, $F(ab')_2$, scF_v and F_v as possible choices for the antibody fragment, A558, col. 21, ln. 33-41, and identifies PEG as a potential polymer. A560, col. 26, ln. 39-40. Gonzalez teaches that conjugates can be made "utilizing any particular type of linkage between an antibody fragment and a polymer," A557, col. 19, ln. 21-24, as well as "using any suitable technique" for "derivatizing antibody fragments with polymers." A557, col. 19, ln. 19-22. In particular, Gonzalez teaches to covalently attach the polymer to a particular amino acid residue or a particular region of the antibody fragment. A557, col. 19, ln. 35-40. On that score, Gonzalez repeatedly prefers the cysteine residue, and even more preferably, the cysteine residue in the hinge region. For example, Gonzalez repeatedly states:

> In such embodiments, the coupling chemistry can, for example, ~~utilize the free sulfhydryl group of a *cysteine residue* not in a~~ disulfide bridge in the parental antibody fragment. A557, col. 19, ln. 40-43. (emphasis added)

> In another embodiment, polymer attachment is targeted to the *hinge region* of the parental antibody fragment. A557, col. 19, ln. 56-57. (emphasis added)
>
> In a preferred embodiment, the conjugate contains an antibody fragment selected from the group consisting of Fab, Fab', and Fab'-SH, wherein every polymer molecule in the conjugate is attached to the *hinge region* of the antibody fragment. A558, col. 21, ln. 36-40. (emphasis added)
>
> In a preferred embodiment, a *cysteine* residue or residues is (are) engineered into the *hinge region* of the parental antibody fragment in order to couple polymer specifically to a selected location in the *hinge region*. A557, col. 19, ln. 62-65. (emphasis added)

Finally, making clear once again his preference for the hinge cysteine, Gonzalez discloses, in his only complete working example, linking PEG to the hinge cysteine of a Fab' heavy chain to make a Fab'-PEG conjugate. A607-609, cols. 120-123, particularly at cols. 122, ln. 64 - col. 123, ln. 3.

D. The Board's Affirmance of the Obviousness Rejections

The Board affirmed the examiner's findings and legal conclusion that Chapman's claims 1-10, 12, 13 and 15 would have been obvious over Gonzalez. A1-18.[2] The Board found that Gonzalez teaches linking two antibody fragments with a polymer to form a "dumbbell-shaped" structure. A6 (FF8); A9. Thus, the Board found that the "only issue -- as recognized by the Examiner -- is whether persons of skill in the art would have had reason to join the fragments

[2] The Board reversed the examiner's anticipation rejection over Gonzalez. A11-14.

together using a polymer linked to the hinge cysteine residue." A9. The Board agreed with the examiner that Gonzalez would have led a skilled artisan to the claimed hinge cysteine because of his repeated preference for linking a polymer there. A9. In particular, the Board found that Gonzalez refers to prior art that establishes that linking a polymer, PEG, to the "hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule." A4-5 (FF2); A9. In addition, the Board found that Gonzalez discloses a complete working example attaching a polymer to the hinge cysteine of the heavy chain. A5 (FF6); A9-10. Based on these disclosures, the Board found that persons of ordinary skill would have recognized the advantages of linking a polymer like PEG to the hinge cysteine to improve the circulating half-life of the antibody fragment and arrived at Chapman's claimed invention. A10.

The Board rejected Chapman's argument that Gonzalez "teaches away" from Chapman's claimed non-disulfide bridge between two heavy chains because Gonzalez expressly discloses that its structures are not limited to "any particular type of linkage between an antibody fragment and a polymer" and thus can be produced by "any suitable technique." A8-9.

The Board also rejected Chapman's hindsight argument, instead finding that Gonzalez' teaching of the dumbbell-shaped structure, together with its

preference for linking a polymer to a hinge cysteine, would have led an ordinarily skilled person to Chapman's claimed invention. A10.

On rehearing, the Board rejected Chapman's repeated "teaching away" and "hindsight" arguments. A21-22. Relying on the explicit disclosure of Gonzalez, the Board again found that one of ordinary skill would have recognized the advantages of coupling a polymer to the hinge cysteine and thereby narrowed the choice for linking the polymer to that site. A21-22. Thus, the Board maintained its obviousness rejection. A19-23.

IV. SUMMARY OF THE ARGUMENT

Substantial evidence supports the Board's fact findings and ultimate legal conclusion that Chapman's divalent antibody fragment would have been obvious. Gonzalez discloses linking two antibody fragments with a polymer to form a dumbbell-shaped structure that is divalent, like a naturally occurring antibody. Separately, Gonzalez repeatedly discloses that the preferred location to attach the polymer to an antibody fragment is the hinge cysteine. Thus, as the Board recognized, the only step that one of skill in the art would have needed to take is to realize that when a polymer is linking two antibody fragments to form a dumbbell, the linkage could be by the preferred hinge cysteine. As the Board properly found, one of skill would have taken that step based on Gonzalez' clear and repeated preference for attachment of the polymer at the hinge cysteine.

Chapman's arguments that the Board misunderstood the "scope and content of Gonzalez" are irrelevant because none of the "errors" that Chapman points to form the basis of the Board's obviousness conclusion. The Board also properly found that Gonzalez does not "teach away." Finally, Chapman's argument that the Board used impermissible hindsight completely ignores Gonzalez' repeated teachings that the hinge cysteine is the preferred attachment site for the polymer.

V. ARGUMENT

A. Standard of Review

Obviousness is a legal conclusion based on underlying fact findings. In re Gartside, 203 F.3d 1305, 1316 (Fed. Cir. 2000). What a reference teaches is a question of fact. Para-Ordnance Mfg. v. SGS Importers Int'l, 73 F.3d 1085, 1088 (Fed. Cir. 1995). Similarly, whether a person of ordinary skill in the art would have been motivated to combine references is a question of fact. Gartside, 203 F.3d at 1316.

This Court upholds fact findings supported by substantial evidence and reviews questions of law de novo. 5 U.S.C. § 706(2)(E); Gartside, 203 F.3d at 1315 (Fed. Cir. 2000). Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." Consol. Edison Co. v. NLRB, 305 U.S. 197, 229 (1938). Where "two different,

inconsistent conclusions may reasonably be drawn from the evidence in record, an agency's decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence." In re Jolley, 308 F.3d 1317, 1329 (Fed. Cir. 2002).

B. The Board Correctly Concluded that Chapman's Claimed Invention Would Have Been Obvious in View of Gonzalez

A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a).

Representative claim 1 recites a divalent antibody fragment with two heavy chains covalently linked by at least one non-disulphide interchain bridge containing a polymer effective for increasing the circulating half-life of the fragment. A272. The polymer bridge links cysteine residues in each heavy chain. A272. Chapman does not dispute the characterization of the claimed antibody fragment-polymer structure as dumbbell-shaped. A284; Br. 20-23.

Gonzalez discloses two antibody fragments linked together by a polymer to form a dumbbell-shaped structure. A565, col. 35, ln. 45-57. Separately, Gonzalez teaches -- repeatedly -- that linking a polymer to the hinge cysteine of an antibody fragment is a preferred embodiment. A557, col. 19, col. 40-43;

A557, col. 19, ln. 56-65; A558, col. 21, ln. 36-40. Gonzalez likewise employs that very hinge cysteine linkage in its only complete working example. A607-609, cols. 120-123, particularly at cols. 122, ln. 64-col. 123, ln. 3. Gonzalez further teaches that linking the polymer PEG to a hinge cysteine of a Fab' fragment produced the advantage of "reduced clearance compared to the parental Fab' molecule." A548, col. 1, ln. 38-43.

Thus, in the examiner's words, which were adopted by the Board, "[t]he only step that one of ordinary skill in the art would need to take is to realize that, when a polymer molecule [is] used to link together two antibody fragments to form a dumbbell-shaped structure," such linkage could be by a polymer linked to the hinge cysteine. A7.

As the Board correctly found, an ordinarily skilled artisan would have taken that step based on the previously described disclosures in Gonzalez, including Gonzalez's repeated preference for the hinge cysteine. A9-10. Hence, substantial evidence supports the Board's fact finding that it would have been obvious to a person of ordinary skill, looking to increase the circulating half-life of an antibody fragment, to have formed the dumbbell-shaped structure by linking two Fab' fragments at the hinge cysteine, thereby meeting the limitations of Chapman's representative claim 1. A10.

C. Chapman's Arguments Fail To Overcome the Board's Obviousness Determination

When the USPTO demonstrates a prima facie case of obviousness, as was done here, the burden shifts to the applicant to show non-obviousness. See In re Rijckaert, 9 F.3d 1531, 1532 (Fed. Cir. 1993). As discussed below, Chapman does not carry his burden.

1. The Board Properly Interpreted The Scope and Content of Gonzalez

Chapman argues that the Board made three statements regarding the "scope and content of Gonzalez" that are "not supported by substantial evidence." Br. 20-23. Chapman's arguments are immaterial because none of the cited statements form the basis of the Board's obviousness rejection. Thus, even if the Board's statements are wrong, any error is harmless. In re Watts, 354 F.3d 1362, 1369 (Fed. Cir. 2004) ("[T]o prevail the appellant must not only show the existence of error, but also show that the error was in fact harmful because it affected the decision below."); Munoz v. Strahm Farms, Inc., 69 F.3d 501, 504 (Fed. Cir. 1995) ("The correction of an error must yield a different result in order for that error to have been harmful and thus prejudice a substantial right of a party.")

First, Chapman argues that the Board erred when it stated, on page A8 of its decision, that "Gonzalez teaches a dumbbell-shaped antibody structure

comprised of two monovalent Fab' fragments and describes linking them via a polymer molecule" because Gonzalez does not explicitly disclose a dumbbell-shaped structure made of any particular Fab fragment. Br. 20. The Board, however, did not base its obviousness rejection on this particular statement. Rather, the Board set forth its obviousness rejection on page A9-10. There, it based its conclusion on Fact Finding 8, which does not restrict the dumbbell-shaped structure to Fab' fragments, stating that

> Gonzalez expressly describes another antibody structure in which 'a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure.' (FF8; Gonzalez, col. 35, ll. 45-57, *see* Ans. 5). This second antibody type is clearly an alternative to the first since Gonzalez states that the polymer joins the two fragments together (FF8), rather than having the polymer hold the heavy and light chains together as for the $F(ab')_2$ described in column 21 (FF7).

A9.

Nothing in this passage, or in Fact Finding 8, refers to a dumbbell-shaped structure comprised of two monovalent Fab' fragments. Hence, Chapman's first argument is a red herring.

Second, Chapman argues that the first sentence of Fact Finding 7 -- that Gonzalez describes "conjugates containing a '$F(ab')_2$ antibody fragment in which the polymer is *attached between* the disulphide bridge that would ordinarily link the heavy and light chains'" -- is not supported by substantial

evidence. Br at. 21-22. Chapman argues that the Board and the examiner misunderstood Gonzalez because Gonzalez does not describe a polymer linking heavy and light chains, but instead a polymer singly attached to one *or* the other chain, but not jointly to both. Br. 22. Again, Chapman's argument is irrelevant because Fact Finding 7 is not the basis of the Board's obviousness rejection. As quoted and explained earlier, the Board based its obviousness rejection on a different embodiment in Gonzalez that is described in Fact Finding 8 – the dumbbell-shaped structure made of two antibody fragments linked by a polymer. A6. Chapman's second argument, therefore, is another red herring.

Finally, Chapman argues that, in Fact Finding 3, the Board erroneously found that Gonzalez limits the antibody fragments that can be used in a dumbbell to three (Fab, Fab' and $F(ab')_2$) when Gonzalez "actually" discloses five possible antibody fragments to use in making an antibody fragment-polymer conjugate. Br. 22-23. As discussed above, the Board's Fact Finding 8, which is the basis of the Board's obviousness rejection, does not limit which fragments can be used in a dumbbell-shaped structure. A6. Chapman's third argument is yet another red herring.

Accordingly, the Board correctly understood the scope and content of Gonzalez when it concluded that Chapman's claimed invention would have been obvious.

2. Gonzalez Does Not "Teach Away"

A reference may be said to "teach away" when a "person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Kubin, 561 F.3d 1351, 1357 (Fed. Cir. 2009), quoting In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Chapman argues that Gonzalez "teaches away" for two reasons. First, Chapman argues that Gonzalez "teaches away" when it "suggests making dumbbell structures using polymer molecules derivatized with 'multiple functional groups' to permit the attachment of two or more antibody fragments to the polymer backbone" and discloses a "variety of crosslinking sites on the antibody fragments" where the polymer could be attached. Br. 23, 24. Chapman argues that the use of multiple functional groups suggests "multiple attachment locations" on the antibody fragments, "not the same location on each heavy chain, much less a cysteine residue on each heavy chain." Br. 23-24.

Chapman's reliance on the multiple functional group teaching is misplaced. As the examiner explained, the purpose of the "multiple functional groups" on the polymer is to attach multiple antibody fragments to a single polymer, not to attach a single antibody fragment at multiple points, along each of its chains, to the polymer. A293. Gonzalez' "rosette" shaped structure,

formed by multiple antibody fragments attached to the polymer, makes this clear. A565, col. 35, ln. 48-57.

Chapman's reliance on the list of crosslinking sites in Gonzalez is similarly misplaced. Br. 24. As the Examiner explained, the crosslinking sites are different ways of attaching the polymer to the antibody fragment. A293. Although Gonzalez teaches theoretically coupling to different groups on the antibody fragment, Gonzalez prefers -- repeatedly -- the cysteine residue in the hinge region and teaches one of skill to engineer the cysteine residue into the hinge region to allow attachment of a polymer at that site. A8; see, e.g., A557, col. 19, ln. 56-65; A557, col. 19, ln. 40-46. What is more, through the only complete working example set forth in the specification, Gonzalez shows in practice coupling at the hinge cysteine when he linked a Fab'-SH fragment to PEG. A9-10; A607-609, cols. 120-123. Hence, rather than "teach away," Gonzalez teaches *towards* Chapman's claimed invention. Moreover, Gonzalez offers this teaching to solve the very problem that Chapman was trying to solve – increasing the circulating half-life of the antibody fragment. A555, col. 15, ln. 15-24.

Second, Chapman argues that Gonzalez "teaches away" because when Gonzalez "discusses attaching a polymer to a divalent antibody fragment, i.e., $F(ab')_2$, it specifically states that disulfide bridges are avoided by substituting

another amino acid for the corresponding cysteine residue in the opposite chain." Br. 24. Chapman takes this disclosure from Gonzalez out of context. Gonzalez' teaching about avoiding disulfide bridges is directed to a linkage between a *heavy* and *light* chain, *not* the *two heavy* chains claimed by Chapman. Chapman even admits as much, essentially defeating his own argument. Br. 24. Additionally, as the Board correctly found, Gonzalez specifically teaches that its antibody structures can be made using "any suitable technique" and any type of linkage. A8; A557, col. 19, ln. 19-24. Thus, the disclosure cited by Chapman would not lead one of ordinary skill in a path divergent from that taken by Chapman.

3. The Board Did Not Use Hindsight

Chapman argues that the Board used impermissible hindsight because it failed to identify the "problem" and "reason to make the claimed invention." Br. 25, 26. The problem, as Chapman defined it, is to modify antibody fragments to prevent them from being easily and rapidly cleared from circulation. A29, ln. 29-35; A322-323. Chapman addresses that problem by site-specific attachment of polymers to antibody fragments. A31, ln. 18-24. Gonzalez addresses, and solves, the very same problem in the very same way – by attachment of polymers to antibody fragments to improve their clearance rate. A558, col. 21, lines 30-34. In addition, Gonzalez identifies a particular

attachment site outside the variable region -- the hinge cysteine -- as a preferred embodiment. A557, col. 19, ln. 62-65. Contrary to Chapman's assertions, the Board's findings recognized both the problem and the reason to make the claimed invention, specifically citing Gonzalez' disclosure that linking PEG to the hinge cysteine of a Fab' fragment "reduced clearance compared to the parental Fab' molecule." A4-5, A9-10; A548, col. 1, ln. 38-43.

Chapman also argues that the Board has provided "no motivation for making the dumbbell-shaped structure described in Gonzalez, much less Chapman's claimed invention." Br. 26. As the Board correctly found, the "teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kahn, 441 F.3d 977, 987-988 (Fed. Cir. 2006); A10-11. Here, the teachings in Gonzalez, including its specific disclosure of a dumbbell-shaped structure, along with its preference for a polymer linked to a hinge cysteine, would have suggested to one of skill in the art to make Chapman's claimed invention. A11.

Chapman next argues that the Board's anticipation analysis "undermines" its obviousness analysis. Br. 28. Chapman is incorrect. The Board reversed the

Examiner's anticipation rejection because Gonzalez does not disclose the dumbbell with cysteine hinge linkage in a single embodiment. A13. That finding, however, does not undermine the Board's obviousness analysis because Gonzalez discloses the dumbbell and teaches that linking a polymer to the hinge cysteine is a preferred embodiment and that linking PEG to the hinge cysteine of a Fab' fragment "reduced clearance compared to the parental Fab' molecule." A557, col. 19, ln. 62-65; A548, col. 1, ln. 38-43. Thus, while Gonzalez did not disclose a specific molecule falling into the scope of Chapman's claim 1 to anticipate, Gonzalez nevertheless leads a skilled artisan directly to Chapman's claimed invention via its separate disclosures, rendering Chapman's claimed invention obvious.

Finally, Chapman argues that even if "obvious to try is the standard applied, the Board must still show that there is a finite number of identified, predictable solutions." Br. 28. At the outset, Chapman's argument is misplaced because the Board did not apply an "obvious to try" standard. A7-11. But, even if one were to apply that standard, Chapman's claimed invention would still be obvious.

Chapman argues that Gonzalez identifies five potential antibody fragments with 500 potential locations on each fragment to attach the polymer, thereby creating an "infinite" number of solutions. Br. 28. Chapman's analysis

is flawed. Even assuming that there are five potential antibody fragments, Chapman's contention of 500 potential attachment locations is based solely on attorney argument. A336. Attorney argument, however, cannot take the place of record evidence. In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997). And, even if attorney argument is accepted as evidence, Chapman fails to appreciate that not all attachment sites are equal. Gonzalez repeatedly teaches throughout the specification and in the only complete working example that the *preferred* site is the hinge cysteine. See, e.g., A557, col. 19, ln. 62-65. As the Board correctly found, these disclosures provide ample reason to make Chapman's claimed invention. A7-11.

This Court's analysis of similar facts in Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007) is relevant here. In Pfizer, the claimed invention was a particular salt. Id. at 1356. Although one prior art reference taught 53 FDA approved anions useful as pharmaceutically acceptable salts, other references identified Pfizer's claimed salt as having several favorable properties. Id. at 1362-63. Based on these disclosures, this Court concluded that Pfizer's salt would have been obvious to make in view of the small prior art genus of anions coupled with the prior art disclosure of the beneficial properties of Pfizer's claimed salt. Id. at 1363. The Court explained: "Taken together, these references provide ample motivation to narrow the genus of 53

pharmaceutically-acceptable anions disclosed by [the prior art] to a few, including" the claimed invention. Id.

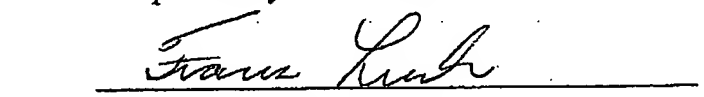
Here, as in Pfizer, Gonzalez provides ample motivation to narrow the list of antibody fragments and attachment sites to arrive at a dumbbell-shaped structure with a polymer linked at a hinge cysteine. Gonzalez teaches a very small genus of antibody fragments. Gonzalez also teaches that the preferred site to link a polymer is a hinge cysteine and exemplifies that preference in the only complete working example in the specification. A607-609, cols. 120-123. Accordingly, it would have been obvious for an ordinary artisan at the time of the invention to settle on Chapman's claimed invention.

VI. CONCLUSION

The Board's decision that claims 1-10 and 12-15 would have been obvious to one of ordinary skill in the art is supported by substantial evidence and correct as a matter of law. Therefore, the Board's decision should be affirmed.

Respectfully submitted,

August 5, 2009



RAYMOND T. CHEN
Solicitor

FRANCES M. LYNCH
JANET A. GONGOLA
Associate Solicitors

P.O. Box 15667
Arlington, Virginia 22215
571-272-9035

Attorneys for the Acting Director of the United States Patent and Trademark Office

CERTIFICATE OF SERVICE

I hereby certify that on August 5, 2009, I caused two copies of the foregoing BRIEF FOR APPELLEE ACTING DIRECTOR OF UNITED STATES PATENT AND TRADEMARK OFFICE to be served by overnight delivery (Federal Express), to Appellant's counsel of record:

Doreen Yatko Trujillo
Cozen O'Connor P.C.
1900 Market Street
Philadelphia, PA 19103

Frances M. Lynch
Associate Solicitor